

Medical Biological Defense Research Program

LTC Harry F. Slife, Jr.
Director
Chemical and Biological Defense Program
Medical S&T Office
United States Army Medical Research & Materiel Command
(USAMRMC)
Fort Detrick, Maryland

Agenda

- ◆ Program Overview
- ◆ Product Development
- ◆ Medical Biological Defense Research Program (MBDRP)
- ◆ Department of Health and Human Services (DHHS) Cooperation
- ◆ Broad Agency Announcement
- ◆ Summary

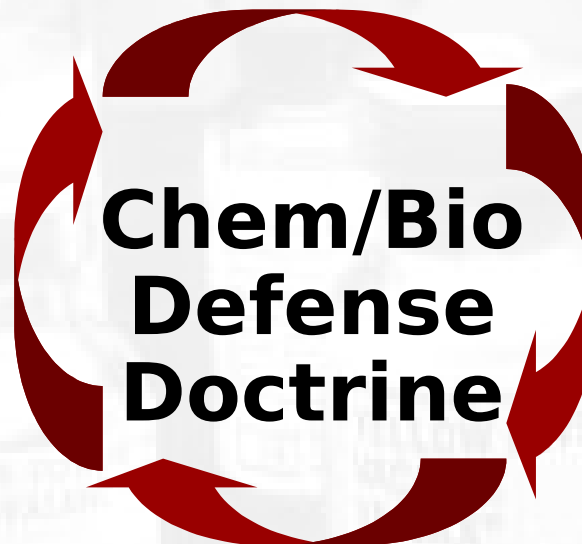
Protecting Warfighters Through Integration and Teamwork

Intelligence

- Agent
- Delivery System
- Organization
- Time

Education and Training

- Military and Civilian Health Care Providers
- Electronic Communication
- Distance Learning



Medical Countermeasures

- Vaccines and Prophylaxes
- Diagnostics
- Therapeutics

Physical Countermeasures

- Detection
- Physical Protection
- Decontamination

Program Direction Process

THREAT ASSESSMENTS

- ◆ Prepared in discrete, tailored packages
- ◆ Evaluate impact on users
- ◆ Define mission needs and service requirements

TEP, STARS, Regional,
Proliferation,
Technology and other
Assessments

REQUIREMENTS

- ◆ Joint Requirements Office for Chemical, Biological, Radiological and Nuclear Defense (JRO-CBRN)
- ◆ Joint Requirements Oversight Council (JROC)

ICDs/CDDs/CPDs,
CPR, Integrated Priority
Lists

PROGRAMS

- ◆ Defense Threat Reduction Agency (DTRA)/Joint Program Executive Office (JPEO)
- ◆ OSD coordinates/integrates funding requests

RDA and
Modernization
Plans, Budget

All programs driven by validated threats and defined mission needs.

Medical CB Defense Research Program

Mission and Vision

- ◆ Provide medical solutions for military requirements to protect and sustain the force in a Chemical & Biological Warfare (CBW) environment



- ◆ Preserve Total Warfighter Effectiveness on a CBW Battlefield
 - Prevent casualties
 - Provide effective treatment of casualties for rapid return to duty
 - Provide rapid, far-forward diagnosis of CBW exposure



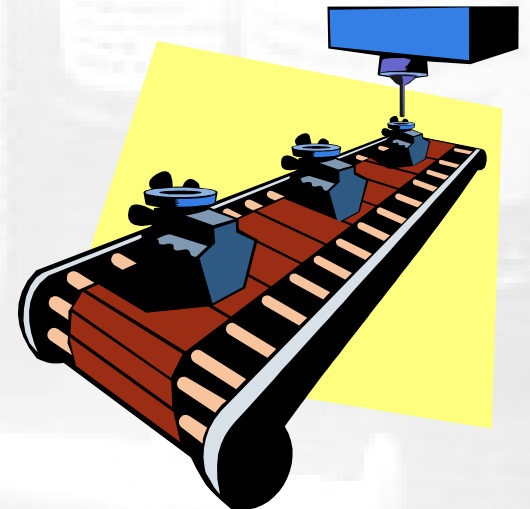
Medical CB Defense Research Program (MCBDRP) Locations



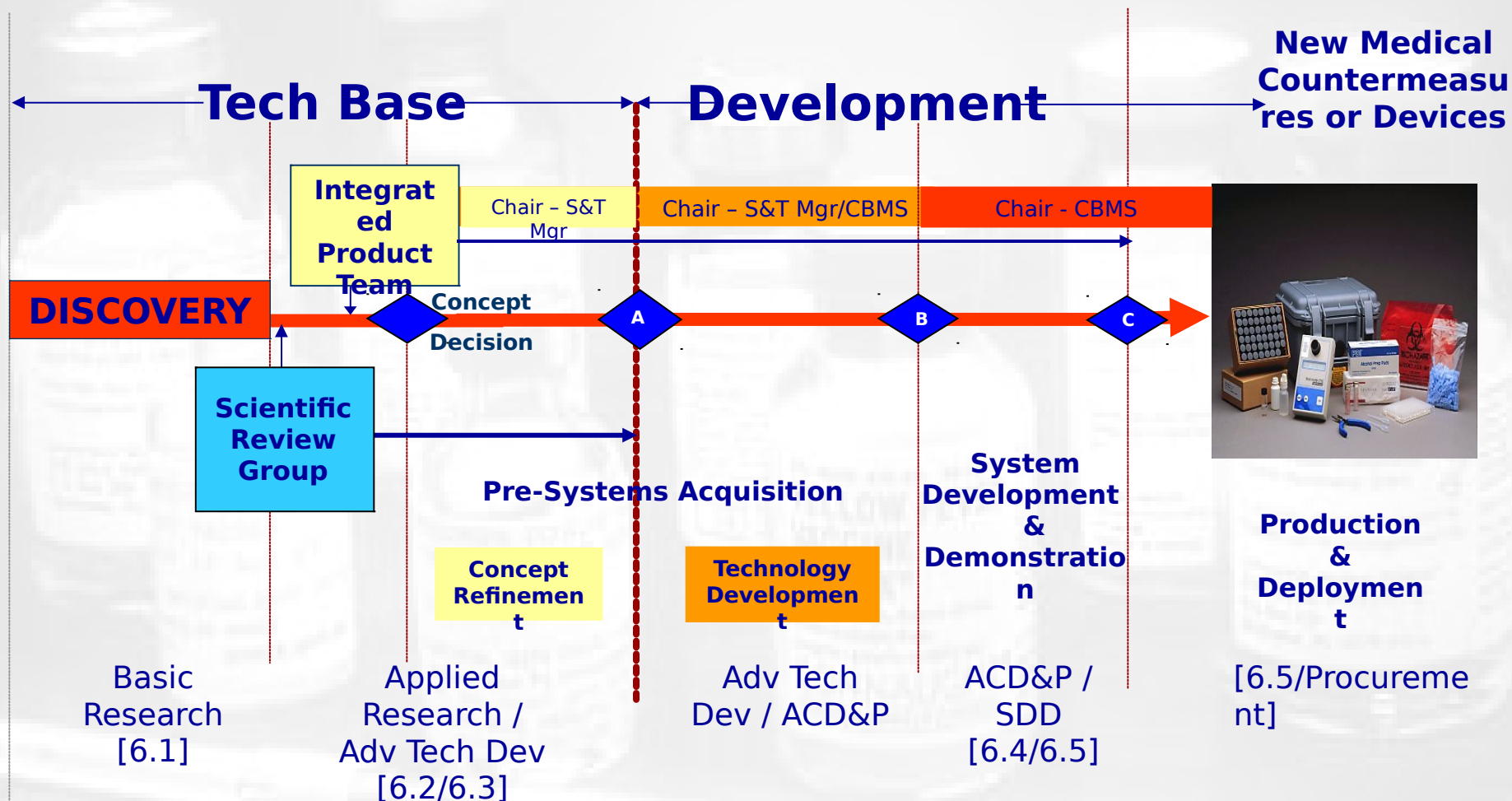
- ◆ Fort Detrick, MD
 - MCBDRP
 - U.S. Army Medical Research Institute of Infectious Diseases
- ◆ Forest Glen Annex, MD
 - Walter Reed Army Institute of Research
 - Naval Medical Research Center
- ◆ Washington D.C.
 - Armed Forces Institute of Pathology
- ◆ Aberdeen Proving Ground, MD
 - U.S. Army Medical Research Institute of Chemical Defense
- ◆ Natick, MA
 - U.S. Army Research Institute of Environmental Medicine

Applied Research Program

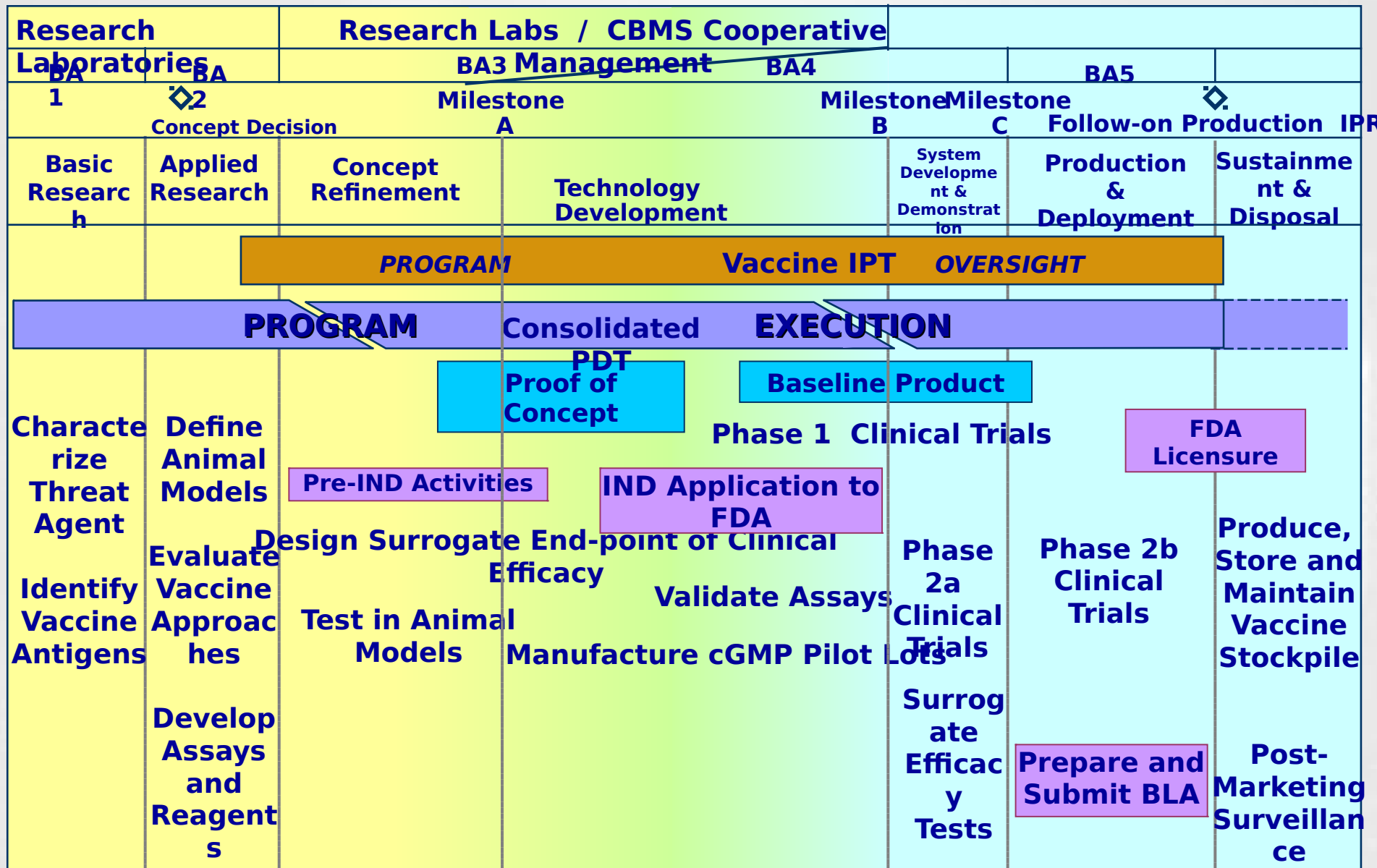
- ◆ Product Oriented
- ◆ Research organized and managed sequentially – Conveyor Belt
- ◆ Plans regularly reviewed
 - Intramural review
 - Extramural review
- ◆ Outcomes evaluated



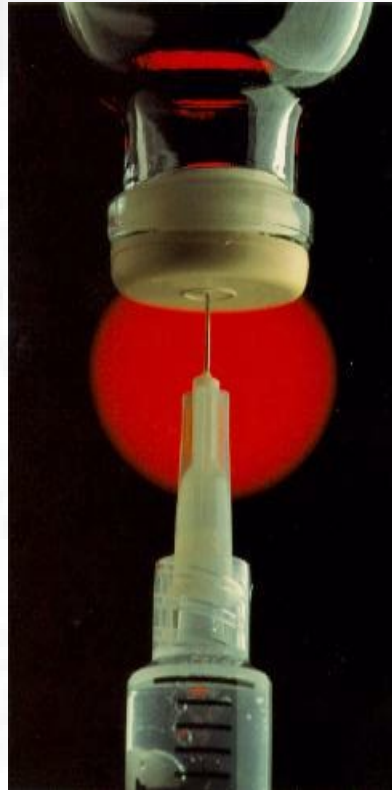
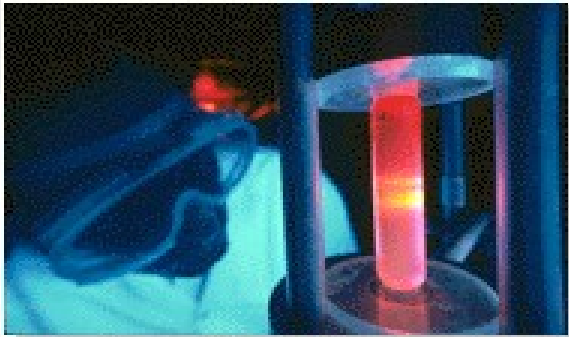
Medical Research and Development Process



Integrating DoD Acquisition and FDA Licensure



Medical Biological Defense Research Program



Potential Threats

◆ Bacteria

- Bacillus anthracis (Anthrax)
- Yersinia pestis (Plague)
- Francisella tularensis (Tularemia)
- Brucella sp. (Brucellosis)
- Burkholderia mallei (Glanders)
- Coxiella burnetii (Q Fever)
- Vibrio cholerae (Cholera)
- Salmonella typhi (Typhus)
- Shigella sp. (Shigellosis)

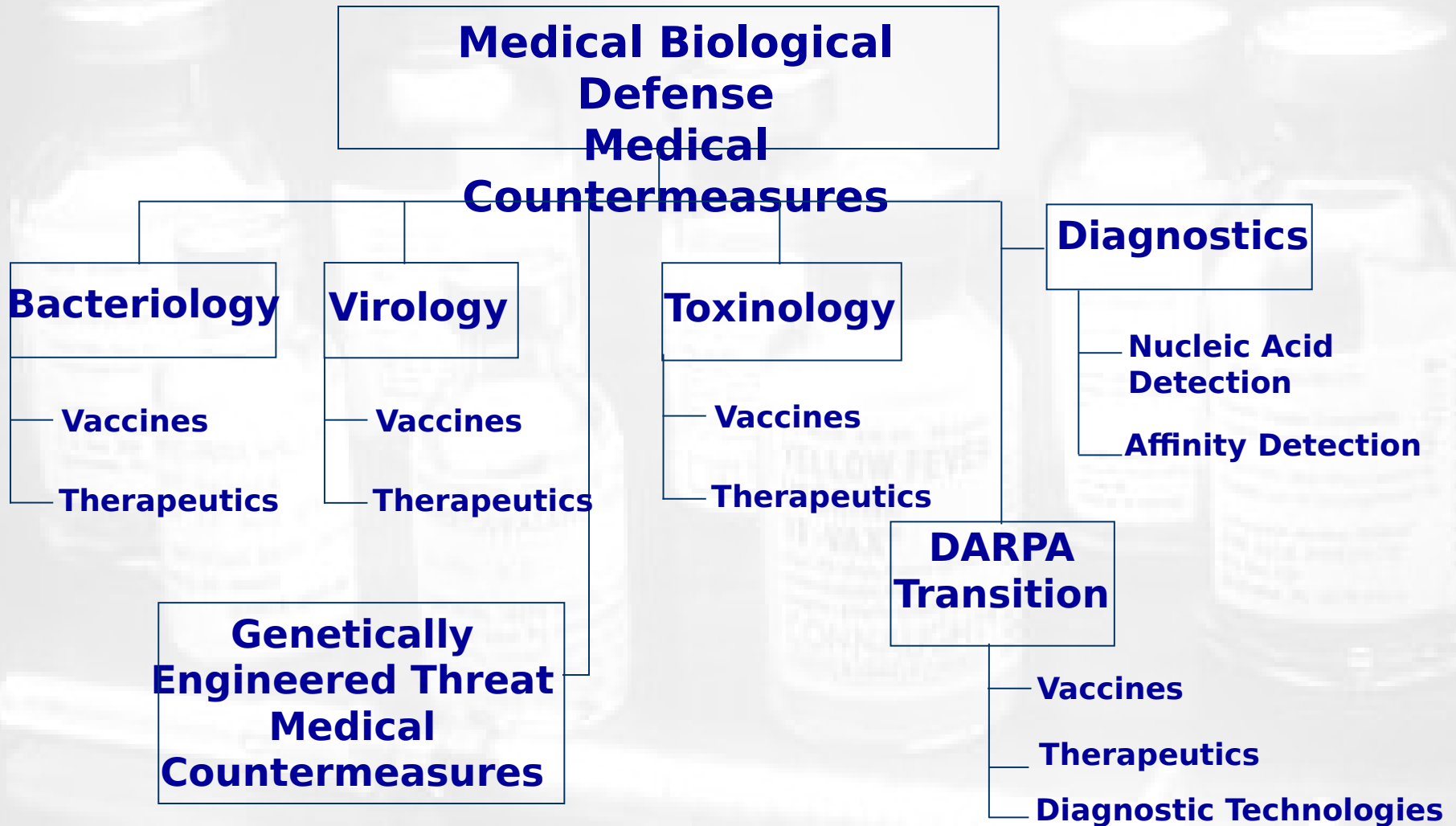
◆ Virus

- Smallpox
- Encephalomyelitis viruses (VEE, EEE, WEE)
- Ebola
- Marburg

◆ Toxin

- Botulinum (Types A – G)
- Staphylococcal Enterotoxins (SEA/B)
- Ricin toxin
- Marine Neurotoxins
- Mycotoxins
- Clostridium perfringens toxins

Research Taxonomy



Medical Biological Defense S&T Focus

Vaccines

Effective against bacterial, viral, and toxin agents

- Bacterial: anthrax, plague, glanders/ melioidosis, and Brucella
- Viral: filoviruses, orthopox viruses, alphaviruses
- Toxins: botulinum, ricin and staphylococcal enterotoxins
- Explore alternative delivery methods and multiagent vaccines

Diagnostics

Deployable, state-of-the-art diagnostic system (reagents, protocols, and devices).

- Nucleic acid-based system
- Improved immunodiagnostic platform
- Common integrated diagnostic system

Challenges

- Threat Assessment
- Pathogenesis/Disease Mechanisms
- “Appropriate” Animal Models
- Immune Responses and Mechanisms
- Surrogate Markers
- Assay Sensitivity and “Appropriate” Reagents

Therapeutics

Antibacterials, antivirals, immunotherapeutics, and other compounds effective against bacterial, viral, and toxin agents

- Bacterial: anthrax, plague, glanders/melioidosis, and Brucella
- Viral: filoviruses and orthopox viruses
- Toxins: botulinum, ricin and staphylococcal enterotoxins

DARPA Transition

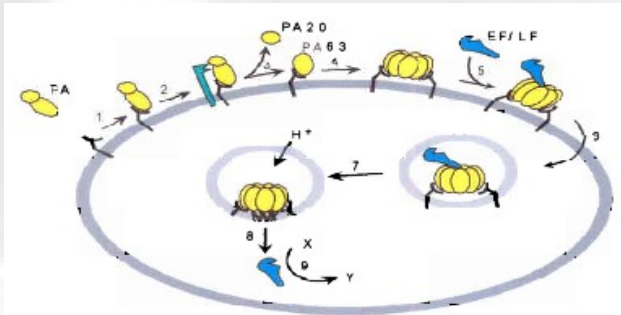
Collaboration with DARPA BW Defense Programs (funded FY01-05)

- Unconventional pathogen countermeasures
- Tissue-based Biosensors

Emerging Medical Biological Defense Products

- ◆ Recombinant Plague Vaccine
- ◆ Next Generation Anthrax Vaccine
- ◆ Multivalent Venezuelan Equine Encephalitis (VEE) Vaccine
- ◆ Recombinant Staphylococcal Enterotoxin Multivalent (SEA/SEB) Vaccine
- ◆ Recombinant Ricin Vaccine
- ◆ Antibiotics and Antiviral Drugs
- ◆ Comprehensive Integrated Diagnostic Systems for BD Threats and Infectious Diseases
 - PCR-based and immunodiagnostic systems
 - Supports program requirements for the Joint Biological Agent Identification and Diagnostic System (JBAIDS)

Bacterial Vaccine Candidates



Assembly and action of anthrax toxin

Recombinant Protective Antigen (rPA) **Anthrax Vaccine:** two vaccine candidates (MRMC and UK)

- MRMC candidate selected for phase 1 clinical trials by National Institute of Allergy and Infectious Diseases (NIAID)
- Both candidates also part of long-term NIAID strategy for 25M dose stockpile for homeland defense

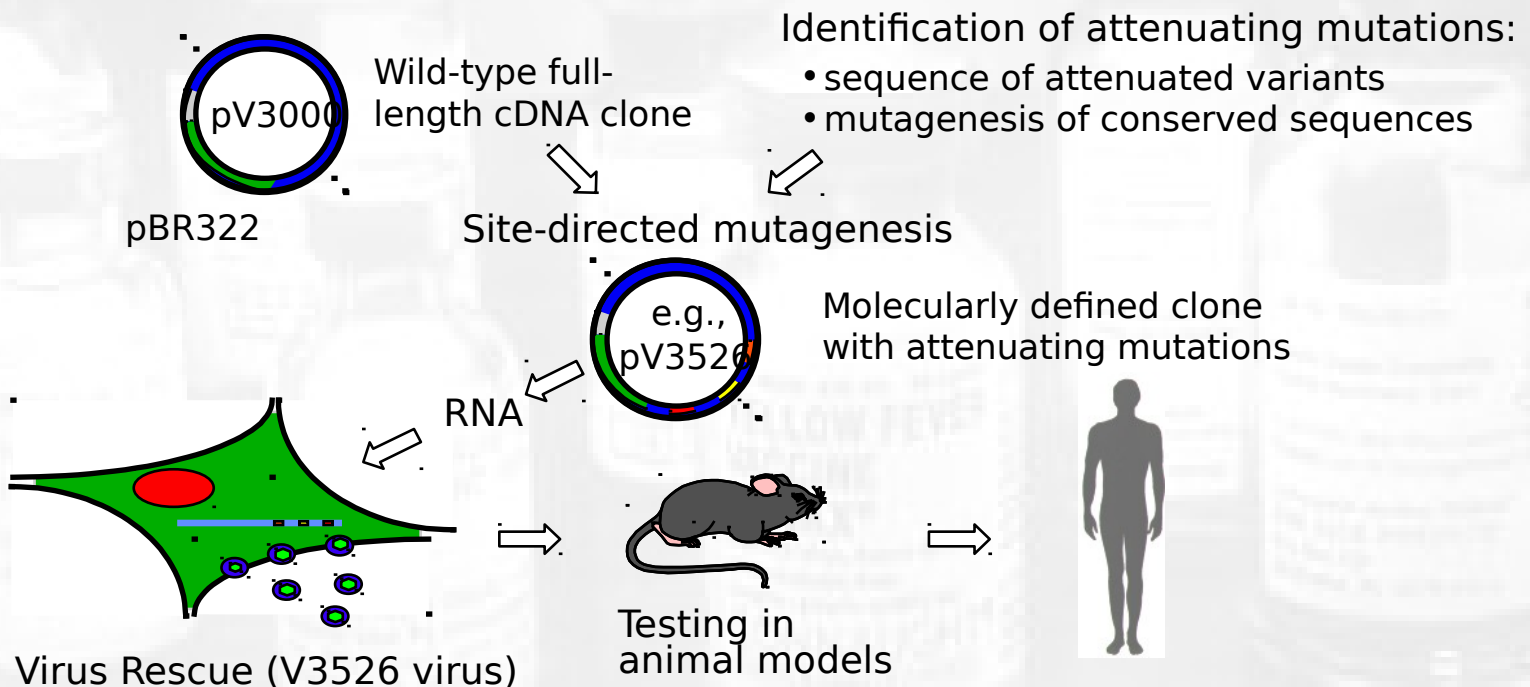
Plague Vaccine: two vaccine candidates (MRMC and UK)

- Both comprised of F1 and V antigens
- MRMC candidate - recombinantly produced fusion protein
- UK candidate - combination of individually produced F1 and V proteins



Viral Vaccine Candidate

**Live attenuated VEE vaccine candidate -
derived by site-directed mutagenesis of a full
length infectious cDNA clone**

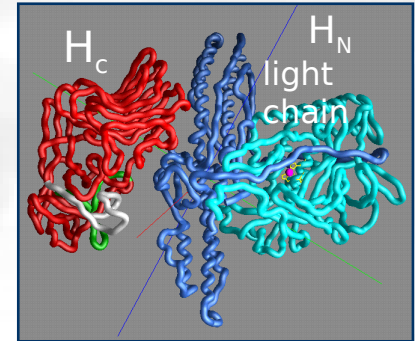


**V3526 candidate demonstrated to protect against
pathogenic VEE virus subtypes of concern (VEE I A/B, IE, &
IIIA)**

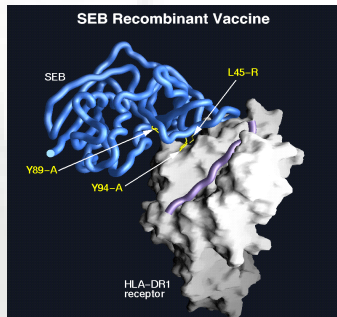
Toxin Vaccine Candidates

Botulinum Neurotoxin (BoTN) Vaccine:

- Vaccine candidate - recombinant protein fragments of botulinum serotypes A and B transitioned in FY00
- Ongoing development of vaccine constructs to protect against BoTN serotypes C, E & F



**Botulinum
Neurotoxin A X-ray
Crystal Structure**

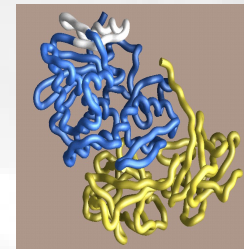


Staphylococcal Enterotoxin (SE) Vaccines: research generated recombinant SE types A and B (SEA/SEB) mutant protein vaccine candidates

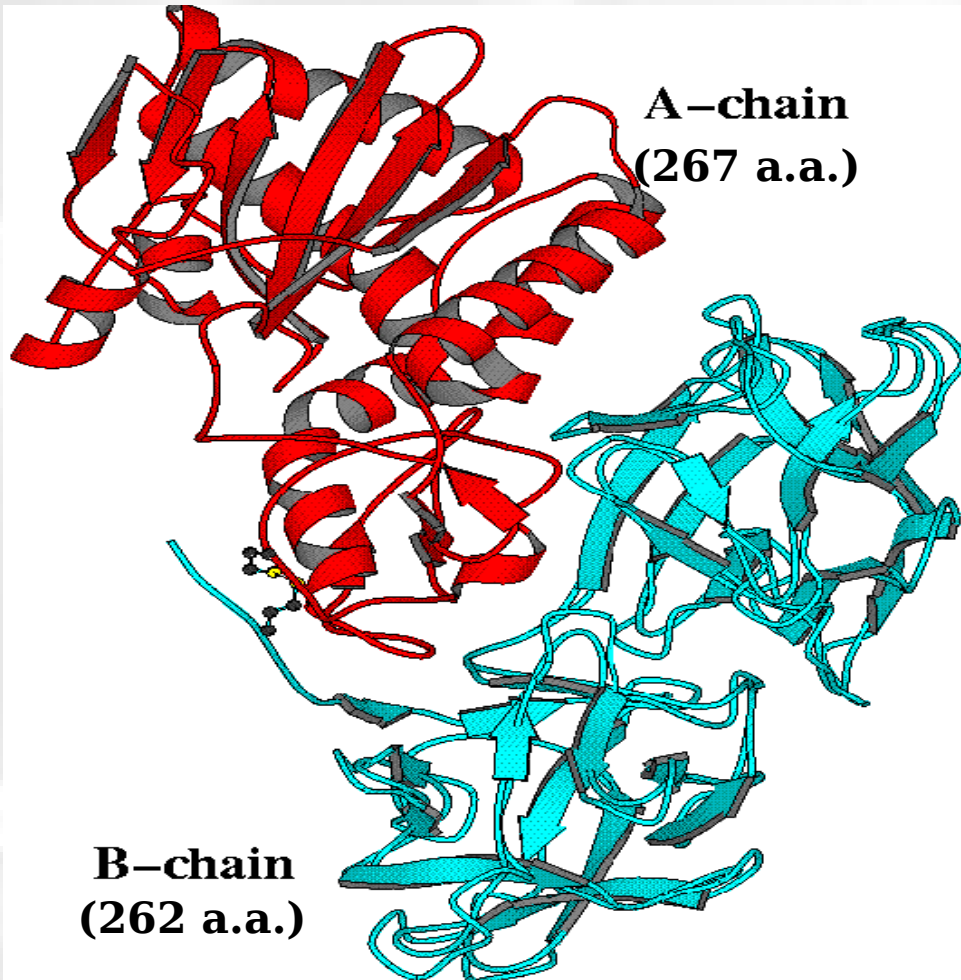
- Demonstrated efficacy of combination vaccine (SEB, SEA) in non-human primates

Ricin: Recombinant expression vectors are being used to produce mutated A-chain immunogens capable of protecting against ricin toxicity

- Classical approaches to a ricin toxoid vaccine proved unsuitable for FDA licensure



Concept: Ricin Toxin



Depurination of A4324 (28S rRNA) disrupts binding of elongation factor (EF2) to the 60S subunit and stops protein synthesis

TECHNICAL PROGRESS TOWARDS COMPLETION:

Designed, expressed, purified and partly characterized ricin vaccine candidates. Lead candidate lacks enzyme activity and protect mice

Therapeutics

Bacterial

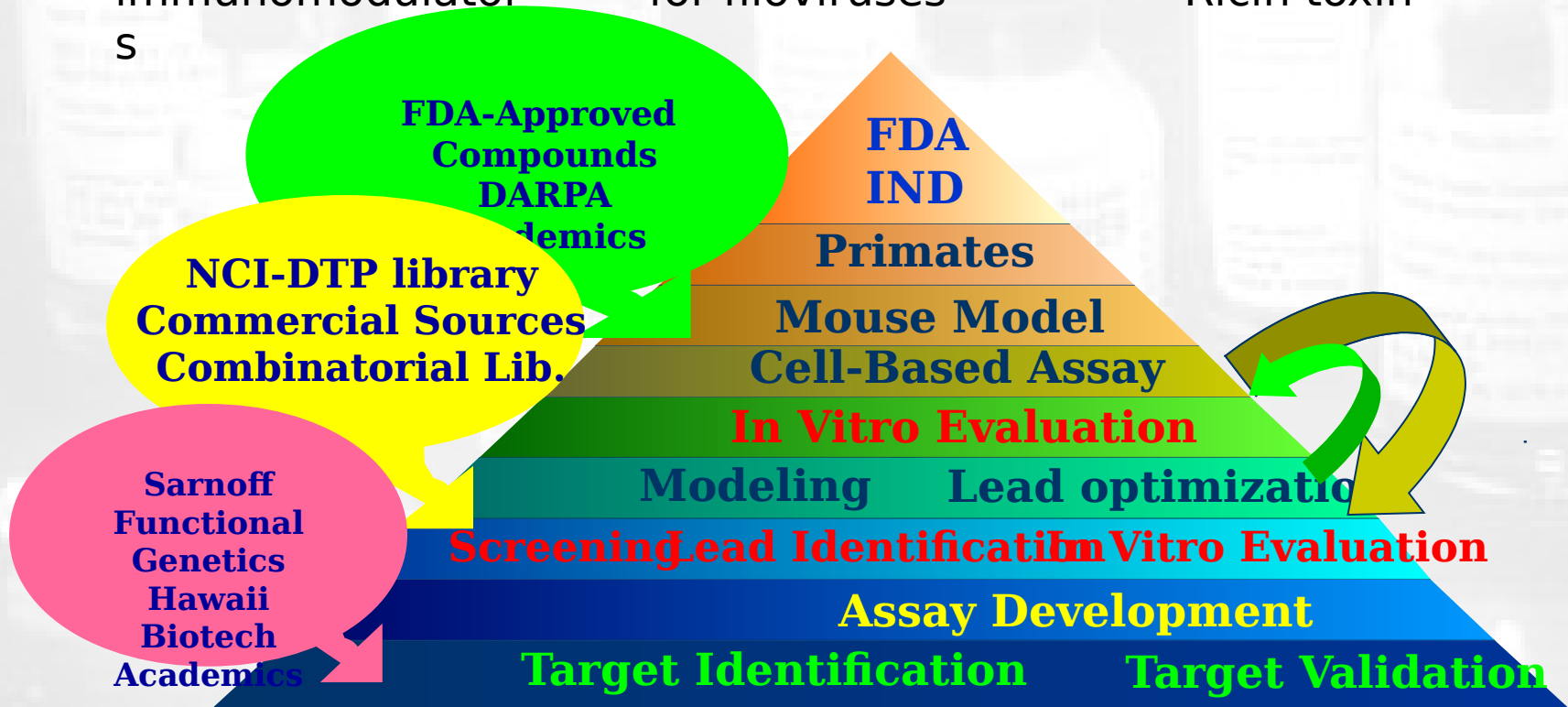
- Licensed antibiotics/ novel antimicrobials
- Immunotherapy/ immunomodulators

Viral

- Antivirals for smallpox (oral) and filoviruses
- Immunotherapies for filoviruses

Toxin

- Botulinum neurotoxins
- Staphylococcal enterotoxins
- Ricin toxin



Medical Diagnostic Technologies

- ◆ Polymerase chain reaction (PCR)-based technologies being developed and fielded
- ◆ Immunodiagnostic platforms as an adjunct to nucleic acid detection (ongoing research)
 - Detection and identification of toxin threats
 - Provides confirmatory assay for other medical diagnostic tests

Technology Options



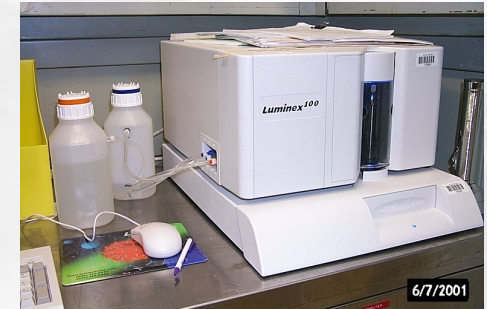
**Time-Resolved
Fluorescence**



Magnetic Field Detection



**Electrochemiluminescence
(ECL) Reaction - First
Generation Device -
ORIGIN®**



Luminex

DARPA Transition Programs

- ◆ Objective: Identify most promising approaches and focus on biological defense program objectives
- ◆ Source: DARPA Unconventional Pathogen Countermeasures and Tissue-Based Biosensors programs
- ◆ Process: (1) DARPA programs presented to MBDRP scientific panels, (2) MBDRP invites solicitations via the Broad Agency Announcement, (3) proposals receive in-house and external peer review, (4) highly rated proposals form basis for initiating contracts.
- ◆ Status: Ten programs selected to date

Future Trends

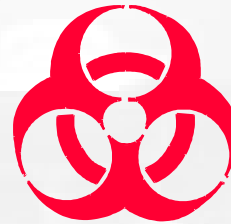
- ◆ Countermeasures for Genetically Engineered Microbes
 - Genomic sequencing of BW threat agents to identify and understand virulence factors, toxins and drug resistance genes
- ◆ Immunomodulators and Therapies
 - Alternatives to agent-specific vaccines or therapies
- ◆ Multiagent Vaccines
 - Alternative to one vaccine for one BW threat agent
- ◆ Alternative vaccine delivery strategies
 - Immunization via mucosal and transdermal

Genetically Engineered Threats

Medical Countermeasures

◆ Concern

- Benign microorganisms genetically altered to produce
 - Toxins
 - Venoms
 - Bioregulators
- Infectious microorganisms genetically altered
 - Antibiotic resistance
 - Enhanced aerosol and environmental stability
 - Defeat standard diagnostic methods



◆ Approach: Bioinformatics

- Compile function-based structural elements that constitute known toxin and virulence factors of BW threats into integrated, searchable databases



Multiagent Vaccines for Biological Threats

- ◆ Goal - vaccine or delivery approach that will concurrently immunize against a range of BW threats
- ◆ Exploit bioengineering and recombinant technologies to achieve vaccines directed against multiple agents
 - RNA Replicon
 - DNA Vaccine

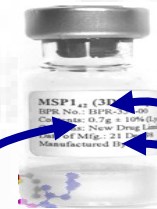
To move away from this...



**25 Shots
Plus Boosters**

To this...

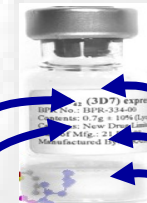
**Botulinum
toxin**



**Marburg Virus
Anthrax**

Or this...

**Ebola-Z
Ebola-S**



**Marburg-Ci67
Marburg-
Musoke
Marburg-Ravn)**

"Panfilovirus vaccine"

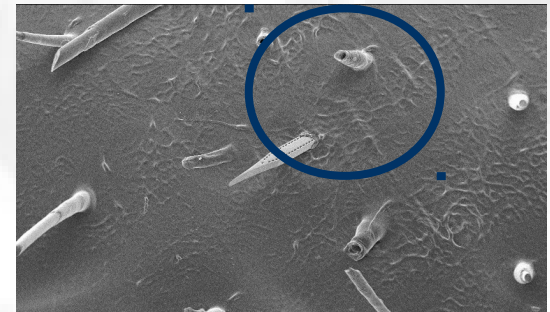
Alternative Vaccine Delivery Methods

- ◆ Goal - respiratory, transdermal, and/or oral immunization that is safe, efficacious and expedient for stimulating mucosal and systemic immunity
- ◆ Simplify administration of multiple vaccines
- ◆ Evaluate multiple novel adjuvants in combination with alternate deliveries

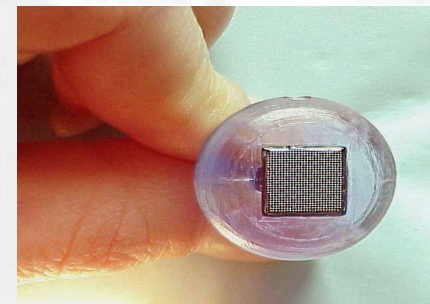
BD Technologies Proprietary Alternate Vaccine Delivery Devices Currently Under Evaluation



SoloVent™



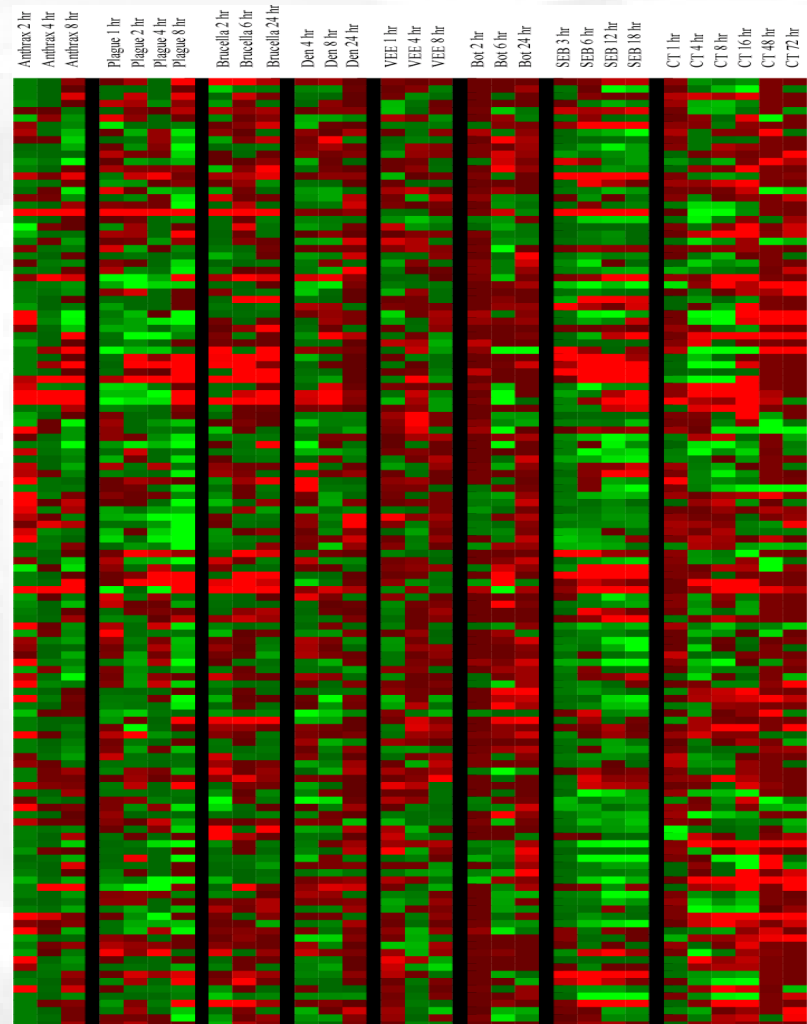
Micromedica™ micro-needles



OnVax™ “swipe and go”

Host Responses to Threat Agents

- ◆ Similarities in host gene expression responses are observed among biothreat agents particularly regarding inflammatory mediators
- ◆ Inflammatory mediators may not differentiate among pathogenic agents, but may be useful markers to gauge illness progression



Cooperation with the Department of Health and Human Services

- ◆ NIAID/CDC/FDA anthrax therapeutics
- ◆ NIAID/USAMRIID/JVAP rPA vaccine candidate clinical trials
- ◆ NIAID/USAMRMC/USAMRIID/NBACC Biodefense Campus
 - Program coordination
 - Program management
 - Infrastructure
- ◆ NIAID/NINDS/USAMRICD counterterrorism initiative
 - Medical chemical defense programs
- ◆ USAMRIID/CDC
 - Smallpox research program
 - Anthrax antibodies

United States Army Medical Research Acquisition Activity

Broad Agency Announcement Website

- ◆ Research Areas of Interest
 - Medical Biological Defense Research Program
 - Medical Chemical Defense Research Program
- ◆ Pre-proposal and proposal submission information
 - **<http://www.usamraa.army.mil>**
 - Open Broad Agency Announcements (BAA) under Business Opportunities
 - Open USAMRMC BAA 02-1 General Information

Summary

- ◆ Medical Biological Defense Research Program
 - DoD program, management by Defense Threat Reduction Agency, Army is Executive Agent
 - Based on threat-driven requirements
 - Product candidates from pretreatment/prophylaxis, vaccine, therapeutic, and diagnostic research areas
 - Extramural collaborations represent a significant portion of the program

? Questions ?

LTC Harry F. Slife, Jr.
Director

Chemical and Biological Defense Program
Medical S&T Office

(301) 619-7439/DSN 343-7439

harry.slife@amedd.army.mil

Back-up Slides

Medical Biological Defense Countermeasures - Licensed or Transition Status

Technology Approach:	Status:
Licensed Medical Biological Defense Products	
<ul style="list-style-type: none">• Vaccines• Post-exposure Prophylaxes• Therapeutics	Licensed Medical Products: <ul style="list-style-type: none">• BioThrax™ Anthrax Vaccine• Dryvax vaccine (1:1 dilution) for smallpox pre- and post-exposure prophylaxis• Ciprofloxacin for anthrax post-exposure prophylaxis and treatment• Penicillin V Potassium and penicillin for anthrax post-exposure prophylaxis and treatment, respectively• Doxycycline for anthrax, plague, Q Fever, and tularemia post-exposure prophylaxis• Doxycycline for anthrax treatment• Gentamicin, doxycycline, streptomycin, tetracycline for plague treatment• Streptomycin, doxycycline, and tetracycline for tularemia treatment• Doxycycline and tetracycline for Q Fever treatment

Medical Biological Defense Countermeasures - Licensed or Transition Status (cont.)

Technology Approach:	Status:
Confirmatory Identification of Pathogens	
<ul style="list-style-type: none"> • Gene Probe - Polymerase Chain Reaction <ul style="list-style-type: none"> - Amplification of select genetic sequences • Development of reagent sets for agent identification and diagnostics 	Advanced Development: <ul style="list-style-type: none"> • Joint Biological Agent Identification and Diagnostic System (JBAIDS) - FY02
Vaccine Candidates	
<ul style="list-style-type: none"> • Identification of potential vaccine candidates • Development and qualification of assays to fully characterize vaccine candidates • Identification of surrogate markers of efficacy • Aerosol challenge studies in animal models 	Advanced Development: <ul style="list-style-type: none"> • Vaccinia, cell culture derived vaccine candidate - FY94 • Tularemia LVS vaccine candidate - FY00 • Venezuelan Equine Encephalitis virus vaccine candidate (V3526) - FY00 • Recombinant botulinum toxin vaccine candidate for serotypes A and B - FY00

Medical Biological Defense Countermeasures - Licensed or Transition Status (cont.)

Technology Approach:	Status:
Vaccine Candidates <ul style="list-style-type: none">• Identification of potential vaccine candidates• Development and qualification of assays to fully characterize vaccine candidates• Identification of surrogate markers of efficacy• Aerosol challenge studies in animal models	
	Technology Development: <ul style="list-style-type: none">• Recombinant fusion antigen (F1-V) plague vaccine candidate MS A in FY04• Staphylococcal enterotoxin A and B vaccine candidates ready for transition in FY02• Recombinant protective antigen (rPA) next generation anthrax vaccine candidate ready for transition in FY03

Transition Planning - Near to Mid-Term

Medical Biological Defense

Thrust Area	Description	TRL 5
BD Vaccines	Recombinant staphylococcal enterotoxin A and B (SEA/SEB) vaccine candidates	FY03
BD Vaccines	Vaccine candidate V3526 (multivalent VEE vaccine candidate)	Entered Technology Development (TD) - Jul 03
BD Vaccines	Recombinant protective antigen (rPA) anthrax vaccine candidate	Entered development at NIAID in FY03
BD Vaccines	Recombinant F1-V plague vaccine candidate	Milestone A in FY04
BD Vaccines	Recombinant ricin vaccine candidate	FY07
BD Vaccine delivery	Alternative vaccine delivery methods for application with rPA, SEB, and F1-V vaccine candidates	Enabling DTO thru FY05. Expect follow-on DTO(s)
BD Diagnostics	<ol style="list-style-type: none"> 1. <u>Immunologically based medical diagnostics</u> (reagents, protocols and devices) 2. Development of Assays as confirmatory tests of other diagnostic systems. 	FY05
BD Diagnostics	<ol style="list-style-type: none"> 1. Nucleic acid detection/diagnostic assays and/or supporting reagents 2. Antigen detection assays and/or supporting reagents 	FY03
BD Therapeutics	Oral form of cidofovir for smallpox pre-/post-exposure treatment	FY08

Transition Planning - Far Term

Thrust Area	Program	Description	TRL 5
BD Vaccines	CB.58 Western and Eastern Equine Encephalitis (WEE/EEE) Vaccine Constructs for a Combined Equine Encephalitis Vaccine	Enabling DTO	FY11 to FY13
BD Therapeutics	CB.59 Therapeutic Strategies for Botulinum Neurotoxins	Enabling DTO	FY11-FY13
BD Vaccines	CB.60 Vaccine Technologies for Protection Against Filovirus (Marburg and Ebola Viruses) Exposure	Enabling DTO	FY11 to FY13
BD Therapeutics	CB.63 Therapeutic Strategies for Treating Filovirus (Marburg and Ebola Viruses) Infection	Enabling DTO	FY11 to FY13

* Enabling DTOs are intended to generate lead candidates/technologies at ~ TRL 3-4. Follow-on Applied Technology DTOs are intended to bring lead candidate/technology to TRL 5.